

DEPARTMENT OF HEALTH AND HUMAN SERVICES**Public Health Service****National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health (NIH), National Toxicology Program (NTP); Notice of an International Workshop on *In Vitro* Methods for Assessing Acute Systemic Toxicity, co-sponsored by NIEHS, NTP and the U.S. Environmental Protection Agency (EPA): Workshop Agenda and Registration Information**

SUMMARY: Pursuant to Public Law 103-43, notice is hereby given of a public meeting sponsored by NIEHS, the NTP, and the EPA, and coordinated by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM). The agenda topic is a scientific workshop to assess the current status of *in vitro* test methods for evaluating the acute systemic toxicity potential of chemicals and to develop recommendations for future research, development, and validation studies. The workshop will take place on October 17-20, 2000, at the Hyatt Regency Crystal City Hotel, 2799 Jefferson Davis Highway, Arlington, VA, 22202. The meeting will be open to the public.

In a previous **Federal Register** notice (Vol. 65, No. 115, pp. 37400-37403), ICCVAM requested information and data that should be considered at the Workshop and nominations of expert scientists to participate in the Workshop. A preliminary list of relevant studies to be considered for the Workshop was also provided. As a result of this request, an ICCVAM interagency Workshop Organizing Committee has selected an international group of scientific experts to participate in this Workshop. NICEATM, in collaboration with ICCVAM, has developed a background summary of data and performance characteristics for available *in vitro* methods. This summary will be made available to invited expert scientists and the public before the Workshop. Requests for the summary can be made to the address given below. This notice provides an agenda, registration information, and updated details about the Workshop.

Workshop Background and Scope**A. Background**

Acute toxicity testing is conducted to determine the hazards of various chemicals and products. This

information is used to properly classify and label materials as to their lethality in accordance with an internationally harmonized system (OECD, 1998). Non-lethal endpoints may also be evaluated to identify potential target organ toxicity, toxicokinetic parameters, and dose-response relationships. While animals are currently used to evaluate acute toxicity, recent studies suggest that *in vitro* methods may also be helpful in predicting acute toxicity.

Studies by Spielmann *et al.* (1999) suggest that *in vitro* cytotoxicity methods may be useful in predicting a starting dose for *in vivo* studies, and thus may potentially reduce the number of animals necessary for such determinations. Other studies (*e.g.*, Ekwall *et al.*, 2000) have indicated an association between chemical concentrations leading to *in vitro* cytotoxicity and human lethal blood concentrations. A program to assess toxicokinetics and target organ toxicity utilizing *in vitro* methods has been proposed that may provide enhanced predictions of toxicity and potentially reduce or replace animal use for some tests (Ekwall *et al.*, 1999). However, many of the necessary *in vitro* methods for this program have not yet been developed. Other methods have not been evaluated in validation studies to determine their usefulness and limitations for generating information to meet regulatory requirements for acute toxicity testing. Development and validation of *in vitro* methods which can establish accurate dose-response relationships will be necessary before such methods can be considered for the reduction or replacement of animal use for acute toxicity determinations.

This workshop will examine the status of available *in vitro* methods for assessing acute toxicity. This includes screening methods for acute toxicity, such as methods that may be used to predict the starting dose for *in vivo* animal studies, and methods for generating information on toxicokinetics, target organ toxicity, and mechanisms of toxicity. The workshop will develop recommendations for validation efforts necessary to characterize the usefulness and limitations of these methods. Recommendations will also be developed for future mechanism-based research and development efforts that might further improve *in vitro* assessments of acute systemic lethal and non-lethal toxicity.

B. Objectives of the Workshop

Four major topics will be addressed:

- *In Vitro* Screening Methods for Assessing Acute Toxicity;

- *In Vitro* Methods for Toxicokinetic Determinations;
- *In Vitro* Methods for Predicting Organ Specific Toxicity; and
- Chemical Data Sets for Validation of *In Vitro* Acute Toxicity Test Methods.

The objectives of the meeting are to:

1. Review the status of *in vitro* methods for assessing acute systemic toxicity:
 - a. Review the validation status of available *in vitro* screening methods for their usefulness in estimating *in vivo* acute toxicity,
 - b. Review *in vitro* methods for predicting toxicokinetic parameters important to acute toxicity (*i.e.*, absorption, distribution, metabolism, elimination), and
 - c. Review *in vitro* methods for predicting specific target organ toxicity;
2. Recommend candidate methods for further evaluation in prevalidation and validation studies;
3. Recommend validation study designs that can be used to characterize adequately the usefulness and limitations of proposed *in vitro* methods;
4. Identify reference chemicals that can be used for development and validation of *in vitro* methods for assessing *in vivo* acute toxicity; and
5. Identify priority research efforts necessary to support the development of mechanism-based *in vitro* methods to assess acute systemic toxicity. Such efforts might include incorporation and evaluation of new technologies, such as gene microarrays, and development of methods necessary to generate dose response information.

Workshop Information

A. Workshop Agenda

Tuesday, October 17, 2000

- 8:30 a.m.—Opening Plenary Session
- Workshop Introduction
 - Welcome from the National Toxicology Program (NTP)
- Overview of ICCVAM and NICEATM
- Acute Toxicity: Historical and Current Regulatory Perspectives
 - Acute Toxicity Data: A Clinical Perspective
- 10:30 a.m.—*In Vitro* Approaches to Estimate the Acute Toxicity Potential of Chemicals
- Estimating Starting Doses for *In Vivo* Studies using *In Vitro* Data
 - An Integrated Approach for Predicting Systemic Toxicity
 - Opportunities for Future Progress
- Public Comment
- Breakout Groups' Charges
- 12:30 p.m.—Lunch Break

1:45 p.m.—Breakout Groups: Identifying What Is Needed from *In Vitro* Methods

- Screening Methods;
 - Toxicokinetic Determinations;
 - Predicting Organ Specific Toxicity and Mechanisms; and
 - Chemical Data Sets for Validation
- 5:30 p.m.—Adjourn for the Day

Wednesday, October 18, 2000

8:00 a.m.—Plenary Session—Status Reports by Breakout Group Co-Chairs

9:00 a.m.—Breakout Groups: Current Status of *In Vitro* Methods for Acute Toxicity

- Screening Methods;
 - Toxicokinetic Determinations;
 - Predicting Organ Specific Toxicity and Mechanisms; and
 - Chemical Data Sets for Validation
- 12:00 p.m.—Lunch Break

1:30 p.m.—Breakout Groups: Current Status of *In Vitro* Methods for Acute Toxicity (Cont'd)

5:30 p.m.—Adjourn for the Day

Thursday, October 19, 2000

8:00 a.m.—Plenary Session—Status Reports by Breakout Group Co-Chairs

9:00 a.m.—Breakout Groups: Future Directions for *In Vitro* Methods for Acute Toxicity

- Screening Methods;
 - Toxicokinetic Determinations;
 - Predicting Organ Specific Toxicity and Mechanisms; and
 - Chemical Data Sets for Validation
- 12:00 p.m.—Lunch Break

1:30 p.m.—Breakout Groups: Future Directions for *In Vitro* Methods for Acute Toxicity (Cont'd)

5:30 p.m.—Adjourn for the Day

Friday, October 20, 2000

8:00 a.m.—Closing Plenary Session—Reports by Breakout Group Co-Chairs

- Screening Methods;
 - Toxicokinetic Determinations;
 - Predicting Organ Specific Toxicity and Mechanisms; and
 - Chemical Data Sets for Validation
- Public Comment

Closing Comments

12:15 p.m.—Adjourn

B. Workshop Registration

The Workshop meeting will be open to the public, limited only by the space available. Due to space limitations, advance registration is requested by October 13, 2000. Registration forms can be obtained by contacting NICEATM at the address given below or by accessing the on-line registration form at: http://iccvam.niehs.nih.gov/invi_reg.htm. Other relevant Workshop information (*i.e.*, accommodations, transportation, etc.) is also provided at this website.

C. Public Comment

The Public is invited to attend the Workshop and the number of observers will be limited only by the space available. Two formal public comment sessions on Tuesday, October 17th and Friday, October 20th will provide an opportunity for interested persons or groups to present their views and comments to the Workshop participants (please limit to one speaker per group). Additionally, time will be allotted during each of the Breakout Group sessions for general discussion and comments from observers and other participants. The Public is invited to present oral comments or to submit comments in writing for distribution to the Breakout Groups to NICEATM at the address given below by October 13, 2000. Oral presentations will be limited to seven minutes per speaker to allow for a maximum number of presentations. Individuals presenting oral comments are asked to provide a hard copy of their statement at registration. For planning purposes, persons wishing to give oral comments are asked to check the box provided on the Registration Form, although requests for oral presentations will also be accepted on-site (subject to availability of time). Persons registering for oral comments or submitting written remarks are asked to include their contact information (name, address, affiliation, telephone, fax, and e-mail).

Guidelines for Requesting Registration Form and Submission of Public Comment

Requests for registration information and submission of public comments should be directed to the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods, Environmental Toxicology Program, NIEHS/NTP, MD EC-17, PO Box 12233, Research Triangle Park, NC 27709; 919-541-3398 (phone); 919-541-0947 (fax); iccvam@niehs.nih.gov (e-mail). Public comments should be accompanied by complete contact information including name, (affiliation, if applicable), address, telephone number, and e-mail address.

References

- OECD (Organisation for Economic Cooperation and Development). (1998). Harmonized integrated hazard classification system for human health and environmental effects of chemical substances. OECD, Paris. (website: <http://www.oecd.org/ehs/Class/HCL6.HTM>)
- Spielmann, H., Genschow, E., Leibsch, M., and Halle, W. (1999). Determination of the starting dose for

acute oral toxicity (LD50) testing in the up and down procedure (UDP) from cytotoxicity data. ATLA, 27(6), 957-966.

- Ekwall, B., Ekwall, B., and Sjorstrom, M. (2000) MEIC evaluation of acute systemic toxicity: Part VIII.

Multivariate partial least squares evaluation, including the selection of a battery of cell line tests with a good prediction of human acute lethal peak blood concentrations for 50 chemicals. ATLA, 28, Suppl. 1, 201-234.

- Ekwall, B., Clemedson, C., Ekwall, B., Ring, P., and Romert, L. (1999) EDIT: A new international multicentre programme to develop and evaluate batteries of *in vitro* tests for acute and chronic systemic toxicity. ATLA 27, 339-349.

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